The Presenilin-1 DeltaE9 Mutation Results in Reduced gamma-Secretase Activity, but Not Total Loss of PS1 Function, in Isogenic Human Stem Cells.

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Public Summary:
This work use genome editing on an iPS model to demonstrate that a disease causing mutation in the Presenilin1 gene contributed to the gain of toxicity.

Scientific Abstract:
Presenilin 1 (PS1) is the catalytic core of gamma-secretase, which cleaves type 1 transmembrane proteins, including the amyloid precursor protein (APP). PS1 also has gamma-secretase-independent functions, and dominant PS1 missense mutations are the most common cause of familial Alzheimer's disease (FAD). Whether PS1 FAD mutations are gain- or loss-of-function remains controversial, primarily because most studies have relied on overexpression in mouse and/or nonneuronal systems. We used isogenic euploid human induced pluripotent stem cell lines to generate and study an allelic series of PS1 mutations, including heterozygous null mutations and homozygous and heterozygous FAD PS1 mutations. Rigorous analysis of this allelic series in differentiated, purified neurons allowed us to resolve this controversy and to conclude that FAD PS1 mutations, expressed at normal levels in the appropriate cell type, impair gamma-secretase activity but do not disrupt gamma-secretase-independent functions of PS1. Thus, FAD PS1 mutations do not act as simple loss of PS1 function but instead dominantly gain an activity toxic to some, but not all, PS1 functions.